reported phenomena. It is recognized that the model used lacks the mathematical rigor and accuracy that would be achieved with the more spatially correct representation of concentration gradients in tissues, as would be defined by diffusion models in series and a convective loss of squamae from the stratum corneum as a result of desquamation. However, the model does provide a simplistic interpretation of events that aids in understanding observed phenomena and in a generalized prediction of likely formation and evidence of a reservoir effect.

## 4.2 WHAT IS THE SKIN RESERVOIR AND WHY IS ITS UNDERSTANDING IN NATURE IMPORTANT?

Topical applications of medications account for about 5% of all products used for therapeutic purposes and may account for more if their cosmetic and cosmeceutic uses are recognized. Most studies on topical products are concerned with the effective penetration of the agents to cause a local or systemic effect or, from an environmental toxicology perspective, their undesirable penetration. What is less well understood is the sequestration of solutes into components of the skin and their rapid release on appropriate provocation of the skin some time later. In some cases, the amount of solute released is sufficient to yield a pharmacological action that replicates that observed when the solute was first applied. This phenomenon is most widely known as the reservoir effect as a consequence of it being used to show the reactivated steroid vasoconstrictor effect when an occlusive dressing was applied to the original steroid application site several weeks after the original application. The reservoir effect is not, however, limited to steroids or to the stratum corneum.

## 4.3 HISTORICAL PERSPECTIVE ON THE STRATUM CORNEUM RESERVOIR FOR DRUGS

The existence of a stratum corneum reservoir for drugs has been expressed in two forms. Vickers (1) has suggested a stratum corneum reservoir because a topical agent such as salicylic acid is excreted in the urine more slowly when applied topically than when injected intradermally (2). One could interpret a reservoir in this context as a function of the time lag associated with a drug diffusing through the skin, the time to reach steady state in the presence of a constant application, and the time to desorb after removal of the application. Hence, in this form, the reservoir is most evident for the more slowly diffusing drugs, i.e., those with long lag times. Schaefer et al. (3) also recognized the importance of the stratum corneum barrier as a determinant of reservoir function. They suggested that the reservoir function was the reciprocal function of the multilayer stratum corneum barrier.

The second form of the reservoir is the recognition that the skin may be a depot for drugs. Malkinson and Ferguson (4) first suggested this concept, but as Vickers (1) points out, their data could be explained by a slow diffusion process through the stratum corneum. Potential sites for this depot were suggested to be keratin spaces, follicular openings, and surface folds (5). The first definitive evidence of a stratum corneum depot for topical corticosteroids was presented by Vickers in 1963 (6). He conducted the experiments shown in Figure 4.1. He showed that the initial vasoconstrictor effects of a topical corticosteroid (fluocinolone acetonide or triamcinolone acetonide) occurring after application and occlusion with Saran film first disappeared within 10 to 16 hours, as expected on removal of the film. The vasoconstrictive effect could be reactivated for up to two weeks after topical application by repeated occlusion of the site. If the stratum corneum was stripped prior to the repeated occlusion, no repeat vasoconstriction is evident, providing evidence that the stratum corneum is the main site for the depot (Figure 4.1). Vickers (1) confirmed this site by showing tape strips of stratum corneum and biopsies from nonstripped epidermal sites had high counts after application of radiolabeled steroids, whereas the biopsy from stripped sites had a low count. Interestingly, the number of counts decreased with successive strips (1), as would be anticipated